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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/389,565	09/03/99	NEVILLE, JR.	D 14028.0290

HM12/1205

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EXAMINER	
VANDER VEGT,F	
ART UNIT	**PAPER NUMBER**
1644	13

DATE MAILED: 12/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/389,565	Applicant(s) Neville et al
	Examiner F. Pierre VanderVegt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Sep 3, 1999*.

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *21-42* ~~is~~/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *21-42* ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5,7,8,11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Notice to Comply with the Sequence Rules

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application is a continuation of application serial number 08/739,703, which claims priority to provisional application 60/008,104. Applicant should amend the specification at page 1 to reflect the current status of the parent application.

Claims 1-20 have been canceled.

New claims 21-42 have been added and are currently pending in this application.

Specification

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The specification discloses the linker sequence $(Gly_4Ser)_3$, for example, at line 29 of page 41 in the written specification. 37 CFR 1.182(c, d and e) put forth a clear requirement for each sequence to be identified by a SEQ ID NO and be represented both in computer readable form (CRF) and on the paper copy corresponding to the CRF. Applicant must provide a substitute CRF, a corresponding paper copy and a new statement that the content of the CRF and the paper copy are the same and that they contain no new matter. See MPEP 2422.03-2422.04.

Appropriate correction is required.

Claim Objections

2. Claim 37 is objected to under 37 C.F.R. 1.821(d) for failing to recite the SEQUENCE ID NO in the claim. Claim 37 recites the amino acid sequence $(Gly_4Ser)_3$ but does not disclose a corresponding SEQ ID NO:.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 21-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999) and Whitlow et al (74A on form PTO-1449 filed December 6, 1999).

The Chaudhary et al reference teaches the construction of single chain anti-Tac (anti-Tac(Fv)) antibodies which are linked to a truncated form of diphtheria toxin (DT388) consisting of the first 388 amino acids of the toxin. Chaudhary et al teaches that this DT388-anti-Tac(Fv) construct is effective in eliminating cells bearing the p55 subunit of the IL-2R. Chaudhary et al teaches that the DT388 truncated form of diphtheria toxin lacks the diphtheria receptor binding site (page 9491 in particular) and therefore cannot indescrimanently bind to and kill cells which do not bear the determinant recognized by the scFv. While Applicant's more specific claims (26 and 31-37) are drawn to a DT390 species consisting of the first 390 amino acids of the toxin, the effect is the same, i.e., the removal of the diphtheria receptor binding site, and the two additional amino acids of DT390 do not appear to confer any special properties beyond the properties of the DT388 polypeptide taught by Chaudhary et al. Therefore, the instantly disclosed and claimed DT390 appears to be obvious over the DT388 of Chaudhary et al, absent a showing of unobvious

properties. Chaudhary et al does not teach an anti-CD3 antibody. Neville et al teaches the use of an immunotoxin conjugate comprising diphtheria toxin and the anti-CD3 antibody UCHT1 for the in vivo treatment of a T cell leukemia in a murine model. It is well known in the art that CD3 is exclusive to and pan-activated T cell, while IL-2R (the anti-Tac target) is not as ubiquitous on activated T cells and is more widely expressed on immune cells, including B cells. Neville et al also teaches that an anti-CD3 antibody-diphtheria toxin conjugate would be effective in the treatment of both graft-versus-host disease (page 2588, paragraph bridging columns in particular), autoimmune disease (page 2588, second column in particular) and AIDS, the latter because anti-CD3 can recognize and kill resting T cells, thereby helping to eliminate latent HIV particles (page 2588, second column in particular). Neville et al teaches whole antibody, not scFv. However, Hirsch et al teaches that anti-CD3 $F(ab')_2$ fragments (lacking the Fc portion of the molecule) are immunosuppressive without the complications sometimes associated with the use of whole molecules anti-CD3 antibodies (Abstract in particular). Hirsch et al further teaches that treatment with anti-CD3 $F(ab')_2$ fragments is effective in the inhibition of the rejection of skin grafts. Whitlow et al teaches that incorporation of antibody variable domains into a single scFv gene simplifies antibody engineering and that engineering an scFv molecule into a fusion protein combines the antigen specificity of the parent antibody with the effector function of the fusion partner (page 97 in particular). Whitlow et al further teaches the GGGGSGGGGSGGGS linker polypeptide (Table 2 in particular) and that linker design and usage is not particularly problematic (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to replace the scFv anti-Tac member of the truncated diphtheria toxin taught by Chaudhary et al with the anti-CD3 member of the immunotoxin taught by Neville et al as an scFv due to the fact that CD3 is a truer marker of T cells and that Hirsch et al teaches that antigen binding fragments of anti-CD3 are preferable over whole molecule and the teachings of Whitlow et al that scFvs simplify production of the antibody-toxin. One would have been motivated with a reasonable expectation of success to combine the teachings based upon the fact that one would want to more specifically target the cells responsible for the etiology of a

subject's condition and the fact that single purification of a fusion protein is faster and more efficient that purification and conjugation of multiple cell products.

4. Claims 21-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al (V on form PTO-892) in view of Neville et al (AJ on form PTO-1449 filed December 6, 1999), Hirsch et al (AS on form PTO-1449 filed December 6, 1999), Whitlow et al (74A on form PTO-1449 filed December 6, 1999) and Youle et al (V on form PTO-892).

The Chaudhary et al, Neville et al, Hirsch et al and Whitlow et al references have been discussed supra. The Youle et al reference is additive to the teachings of Neville et al regarding the use of UCHT1-diptheria toxin conjugates for the treatment of graft-versus-host disease (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use anti-CD3 conjugated with truncated diphtheria toxin for the reasons above and awould be further motivated with a reasonable expectation of success by the teaching of Youle et al anti-CD3-diptheria toxin was more effective and efficient at killing T cells than other antibody/toxin combinations.

Conclusion

5. Reference 15A on form PTO-1449 filed December 6, 1999 has been lined through and not considered because the reference was supplied in German without a certified translation and the document does not contain an English abstract.

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in

the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Tuesday through Friday and odd-numbered Mondays (on year 2000 366-day calender) from 6:30 am to 4:00 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
Technology Center 1600
December 4, 2000

F. PIERRE VANDERVEGT
PATENT EXAMINER